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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,298	PHILLIPS ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 28-34* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 05/04/2009 has been entered. Claims 21-27 are cancelled. Claims 28-34 are newly added. Claims 1-20 and 28-34 are pending. Claim 1 is amended.

This application 10/567,298 is a 371 of PCT/US04/26195 filed on 08/11/2004 which claims benefit of 60/494,184 filed on 08/11/2003, and claims benefit of 60/494,185 filed on 08/11/2003, and claims benefit of 60/513,067 filed on 10/21/2003, and claims benefit of 60/513,657 filed on 10/23/2003.

Election/Restriction

Newly added independent claim 28 filed on 05/04/2008 is directed to a modified mammalian tissue, wherein said tissue comprises a genetically modified mammalian stem or progenitor cell, wherein said cell comprises: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product. Claims 29-34 depend from claim 28. It is noted the tissue of claims 28-34 comprises the same "genetically modified stem or progenitor cell" as recited in claim 1 (See limitations (a) and (b) of claims 1 and 28). Therefore, claims 28-34 are included as part of elected invention, Group I.

With regard to the election of hypoxia as the single physiological stimulus from claim 19, as documented on pages 2-3 of the office action mailed on 02/04/2009, it is worth noting that the

election of hypoxia as a species reads on the species listed in claim 18 that include hypoxia, glucose, a tumor marker, and an atherosclerosis indicator of inflammation. As hypoxia and glucose are two distinct species of physiological stimuli that lead to distinct physiological responses, the limitation "wherein said physiological stimulus- sensitive chimeric transactivator comprises a glucose-sensitive element" recited in claim 20 reads on non-elected species "glucose" recited in claim 18. Accordingly, claim 20 is not readable on elected species "hypoxia" recited in claims 18 and 19. Accordingly, claim 20 is withdrawn for recitation of non-elected species.

It is worth noting that Applicants elected heme oxygenase-1 (HO-1) as the single therapeutic product from claim 7, mesenchymal stem cell (MSC) as the single cell from claim 13, cardiac cell as the single cell from claim 14 (See page 2 of office action mailed on 02/04/2009). Accordingly, the species "a bone marrow mesenchymal progenitor cell (MPC)" recited in claim 13 and the limitation "progenitor cell" recited in amended claim 1 are considered as non-elected species. Therefore, amended claim 1 and newly added claim 28 are examined to the extent of "mesenchymal stem cell (MSC)" with respect to the limitation "a genetically modified stem or progenitor cell".

Claims 21-27 are cancelled. Claims 1-20 and 28-34 are pending. Claim 1 is amended.

Claims 20 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Claims 1-19 and 28-34 are currently under examination to the extent of elected species, which are (i) mesenchymal stem cell (MSC), which has the capacity to differentiate into a

cardiac cell, with respect to a genetically modified stem or progenitor cell, and (ii) heme oxygenase-1 (HO-1) gene with respect to a nucleic acid sequence encoding a therapeutic product, and (iii) hypoxia with respect to a physiological stimulus.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Previous rejection of claim 17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because Applicant's arguments filed on 05/04/2009 have been fully considered and they are found persuasive.

2. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 05/04/2009.*

Amended claim 1 filed on 05/04/2009 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

Claim 14 depends from claim 1 and recites "wherein said cell is selected from the group consisting a cardiac cell, muscle cell, ---", which Applicant elected cardiac cell as a species. It is noted that a genetically modified stem cell recited in claim 1 cannot be a cardiac cell at the same time becasue a stem cell is a pluripotent or multipotent cell that can be further differentiated whereas a cardiac cell is a differentiated cell already.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Previous rejection of claims 1-9, 11, and 14-19 under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 05/04/2009 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous

polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

Neither Tang et al. (2002) nor Juan et al. (2001) teaches a genetically modified stem or progenitor cell.

4. Previous rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001), as applied to claims 1-9, 11, and 14-19 above, and further in view of **Nicklin et al.** (Nicklin et al., Tropism-modified adenoviral and adeno-associated viral vectors for gene therapy, *Curr Gene Ther.* 2(3):273-93, 2002), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 05/04/2009 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

None of Tang et al., Juan et al. and Nicklin et al. teaches a genetically modified stem or progenitor cell.

5. Claims 12 and 13 remain rejected, claims 1-9, 11, and 14-19 previously rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (2002) in view of Juan et al. (2001), and newly added claims 28-34, are rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. *J Gene Med.* 3(3):240-51, 2001) and **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25, 2001). Applicant's arguments filed 05/04/2009 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 10-11 of the office action mailed on 02/04/2009. *The inclusion of claim 1-9, 11, 14-19, and 28-34 in this maintained rejection is necessitated by claim amendments filed on 05/04/2009.*

For the clarity and completeness of this office action, the rejection for the reasons of record advanced on pages 10-11 of the office action mailed on 02/04/2009, is reiterated below with revisions addressing claim amendments filed on 05/04/2009. In this regard, it is noted that the order of citation of references Turgeman et al. and Juan et al. in this maintained rejection has been switched to address the recitation of stem cell in claim 1.

Amended claim 1 filed on 05/04/2009 reads as follows: A genetically modified stem or progenitor cell comprising: (a) a first exogenous polynucleotide comprising a gene

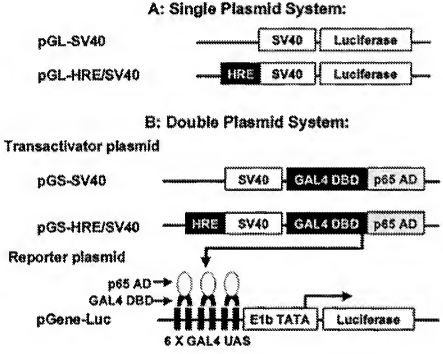
switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

Newly added claim 28 reads as follows: A modified mammalian tissue, wherein said tissue comprises a genetically modified mammalian stem or progenitor cell, wherein said cell comprises: (a) a first exogenous polynucleotide comprising a gene switch/biosensor, wherein said gene switch/biosensor encodes a physiological stimulus-sensitive chimeric transactivator and an operatively linked promoter; and (b) a second exogenous polynucleotide comprising a gene amplification system, wherein said gene amplification system comprises a nucleic acid sequence encoding a therapeutic product.

Claim interpretation: The limitation "wherein said therapeutic product is a polypeptide that is endogenous to said cell" recited in claim 17 is interpreted as any therapeutic product that is a polypeptide encoded by a transgene (i.e. exogenous polynucleotide) and the genome of said cell comprises gene(s) on chromosomes that can encode the same polypeptide (which is considered endogenous to the said cell). The limitation "A modified mammalian tissue recited in claim 28 reads on (i) a mammalian tissue differentiated from the recited genetically modified mammalian stem cell, and (ii) a mammalian tissue comprises the recited genetically modified mammalian stem cell, which is transplanted to an existing mammalian tissue.

With regard to the limitations of claims 1-6, 8, 11, 12, 14-19, and newly added claims 28-34 of instant application, Tang et al. teaches that coronary artery disease frequently involves

repeated bouts of myocardial ischemia (which reads on hypoxia recited in claims 18, 19, and 33), and to automatically up-regulate the cardioprotective transgenes under hypoxic ischemia, a "vigilant vector" gene therapy system was developed and tested in a rat embryonic cardiac myoblast (H9c2, which reads on limitation cardiac cell recited in claim 14 of instant application). Tang et al. teaches that, in the vigilant vector, a hypoxia response element-incorporated promoter was used as a switch to turn on the gene expression in response to hypoxic signal. Furthermore, Tang et al. teaches that a novel double plasmid system was designed to elevate the potency of the vigilant vector, and instead of putting the promoter and the reporter gene in the same plasmid (single plasmid system), Tang et al. separated them into two plasmids: the transactivator plasmid and reporter plasmid (double plasmid system). Tang teaches that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain (which reads on the limitations of claim 6 of instant application), and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene (See abstract and Figure 1 shown below, Tang et al., 2002).



It is noted that with regard to the limitation recited in claim 15 "wherein said gene amplification system comprises nucleic acid sequences encoding multiple therapeutic products are the same or different", this limitation reads on over-expression of the same gene resulting from transactivator binding to the UAS (upstream activation sequences) of the gene as taught by Tang et al.

Tang et al. does not teach (I) a genetically modified stem cell recited in claim 1 and a mesenchymal stem cell (MSC) recited in claims 13 and 34, and (II) a nucleic acid sequence encoding a therapeutic product recited in claim 1 and said therapeutic product being heme oxygenase-1 (OH-1) recited in claim 7 and adenovirus recited in claim 9 of instant application, and (III) a modified mammalian tissue recited in claim 28 and its dependent claims 29-33.

(I) Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types. Turgeman et al. teaches that

hMSCs represent a novel platform for skeletal gene therapy and that hMSCs can be genetically engineered to express desired therapeutic proteins inducing specific differentiation pathways (See abstract, page 240, Turgeman et al.).

(II) Juan et al. teaches the followings: (i) adenovirus-mediated gene transfer of HO-1 (which reads on claims 9 and 32 of instant application) in arteries reduces iron overload and inhibits lesion formation in apolipoprotein E (apoE)-deficient mice (See abstract, Juan et al., 2001), and (ii) heme oxygenase (HO) is a rate-limiting enzyme in heme catabolism; one of the isozymes, HO-1, is a stress-response protein and can be induced by a variety of oxidation-inducing agents, including heme/hemoglobin, heavy metals, UV radiation, cytokines, and others, and induction of HO-1 leads to the degradation of pro-oxidant heme to carbon monoxide (CO) and biliverdin (See introduction, page 1519, Juan et al., 2001).

(III) With regard to the limitation "a modified mammalian tissue" recited in claim 28, the limitation "a human cell" recited in claim 29, the limitation "said cell is autologous to said tissue" recited in claim 30, and the limitation "mesenchymal tissue" recited in claim 31, Turgeman et al. teaches that genetically engineered hMSCs displayed enhanced proliferation and osteogenic differentiation in culture; *in vivo*, transplanted genetically engineered hMSCs were able to engraft and form bone and cartilage in ectopic sites, and regenerate bone defects (non-union fractures) in mice radius bone; and importantly, the same results were obtained with hMSCs isolated from a patient suffering from osteoporosis (See abstract and Figure 4, Turgeman et al., 2001). It is noted that the formation of new bone and cartilage in ectopic sites comprising cells differentiated from hMSCs taught by Turgeman et al. (2001) reads on the

limitation "mesenchymal tissue" recited in claim 31, and the limitation "said cell is autologous/syngenic to said tissue" recited in claim 30.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of (i) Tang et al. regarding a genetically modified/transfected cell comprises two plasmids: the transactivator plasmid and reporter plasmid and that that the hypoxia response element (HRE)-incorporated promoter increased the expression of a chimeric transcription factor consisting of the yeast GAL4 DNA binding domain and the human nuclear (transcription) factor-kappaB (NF-kappaB) p65 activation domain, and the chimeric regulator binds specifically to the upstream activating sequence for GAL4 in the reporter plasmid and activates the transcription of the transgene, with the teachings of (ii) Turgeman et al. regarding the use genetically engineered hMSCs for gene therapy to express desired therapeutic proteins, whereas the hMSCs can be directed to specific differentiation pathways to form mesenchymal tissue, and the teachings of (iii) Juan et al. regarding expressing HO-1 gene from an adenoviral vector for therapeutic purpose, to arrive at the claimed genetically modified stem cell comprising expression cassette as recited in claims 1-9 and 11-19 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Tang et al., Turgeman et al., and Juan et al. because (i) Tang et al. establishes the double plasmid system sensitive to hypoxia condition for gene therapy of coronary artery disease by monitoring the expression of luciferase as a reporter, (ii) Turgeman et al. teaches that human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types and hMSCs can function as a transgene vehicle and can be genetically

engineered to express desired therapeutic proteins and the genetically engineered hMSCs can be induced toward specific differentiation pathways to form mesenchymal tissue for treatment, and (iii) Juan et al. teaches Adv-OH-1 construct (which expresses OH-1 from an adenoviral vector) for gene therapy of atherosclerosis since HO-1 is a stress-response protein and can be induced by a variety of oxidation-inducing agents. Furthermore, substitution of a reporter gene with a gene encoding a therapeutic protein in the context of a vector, either a plasmid or a viral vector, is a common practice in molecular biology depending on the gene of interest to be expressed.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoplast cell line by the teachings of Tang et al., (ii) demonstration of genetically engineered human mesenchymal stem cells expressing human BMP-2 from an adenoviral vector leading to formation of cartilage and bone *in vivo* for treatment of osteoporesis by the teachings of Turgeman et al., and (iii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and response to Applicant's arguments

Applicant argues that Applicant's claimed invention advantageously provides for cell therapy wherein a patient can have their own stem or progenitor cells prepared from their own tissue (e.g., bone marrow) and then the cells can be provided with a vector (e.g., hypoxia gene switch/transgene) outside the body before injecting the modified cells directly into the target tissue (e.g., heart) of the patient. Applicant argues that the claimed invention provides cells, such

as adult stem cells derived from bone marrow, a novel means of surviving in a hostile environment (such as in an injured heart where oxygen levels are very low). Applicant states that it was not obvious to provide cells with means for surviving in the hostile environment because the high rate of death of implanted stem cells was not known in the art at the time of the present invention; when bone marrow stem cells are transplanted into ischemic hearts, the majority of the engrafted cells (over 90%) die within 1-2 days, and the present invention solved the problem of poor cell survival that occurs in stem cell therapy. Applicant argues that the Tang et al. reference does not teach or suggest anything of relevance in regard to the problem of implanted stem cell survival. Applicant states that the Tang et al. reference describes testing different types of gene switches, including single vector and double vector models; the rat myoblast cell line H9c2 referred to in the Tang et al. reference was only used for testing the vector; and it was not used for stem cell transplantation. Applicant argues that nowhere in the Tang et al. reference did the authors teach or suggest an approach for improving stem cell survival in therapy (See page 10 of Applicant's remarks filed on 04/05/2009).

In response, the Examiner notes that the intended use of a product does not bear patentable weight for art rejection. In this instance, Applicant's arguments that the intended use of the genetically modified stem cell are for surviving in the hostile environment (such as in an injured heart where oxygen levels are very low) and for stem cell transplantation into ischemic hearts have been fully considered and they are found not persuasive. This is because the intended uses of the genetically modified stem cell do not bear patentable weight for prior art rejection in examination of patentability of claimed genetically modified stem cell.

With regard to the relevance of primary reference by Tang et al. to the claimed invention, it is worth noting that Tang et al. (2002) is Applicant's own paper published more than one year before the claimed priority date of instant application (i.e. with 102(b) date). Additionally, the disclosed hypoxia inducible double plasmid system for myocardial ischemia gene therapy by Tang et al. (2002) is certainly and directly related to Applicant's arguments pertaining to the intended use of genetically modified cell. The Tang et al. (2002) reference utilizes cardiac myoblast cell, which is certainly relevant to the disclosure by Turgeman et al. regarding human mesenchymal stem cells (hMSCs) are pluripotent cells that can differentiate to various mesenchymal cell types, and hMSCs can be genetically engineered to express desired therapeutic proteins inducing specific differentiation pathways. Furthermore, it is worth noting that the maintained 103 rejection is relied on the combined teachings of cited references as a whole being *prima facie* obvious. Applicant's arguments addressing the deficiency of each cited reference have been fully considered and found not persuasive.

Furthermore, with regard to the asserted requirement for teaching, suggestion, or motivation to render obviousness, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner also notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine The Tang et al.

(2002), Turgeman et al. (2001), and Juan et al. (2001) has been clearly set forth on pages 10-11 of the Non-Final office action mailed on 02/04/2009, and revised above to address claim amendments in this office action.

6. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Tang et al.** (Tang et al. Hypoxia inducible double plasmid system for myocardial ischemia gene therapy, *Hypertension*, 39(2 Pt 2):695-8, 2002; this reference is cited as reference R40 on the IDS filed by Applicant on 04/06/07) in view of **Turgeman et al.** (Turgeman et al., Engineered human mesenchymal stem cells: a novel platform for skeletal cell mediated gene therapy. *J Gene Med.* 3(3):240-51, 2001) and **Juan et al.** (Juan et al, Adenovirus-mediated heme oxygenase-1 gene transfer inhibits the development of atherosclerosis in apolipoprotein E-deficient mice, *Circulation*, 104(13):1519-25,2001), as applied to claims 1-9 and 11-19 above, and further in view of **Nicklin et al.** (Nicklin et al., Tropism-modified adenoviral and adeno-associated viral vectors for gene therapy, *Curr Gene Ther.* 2(3):273-93, 2002). *This rejection is necessitated by claim amendments filed on 05/04/2009, which recite stem cell in claim 1.*

The teachings of Tang et al., Turgeman et al., and Juan et al. have been discussed in the preceding section of the rejection of claims 1-9 and 11-19 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. in view of Turgeman et al. and Juan et al.

None of Tang et al., Turgeman et al., and Juan et al. teaches adeno-associated virus as a vector recited in claim 10.

Nicklin et al. et al. teaches that advances in vector targeting strategies have been rapid within the field of DNA-based viruses, particularly adenovirus (Ad) and more recently adeno-

associated virus (AAV) based vectors, and both Ad and AAV vectors can be modified in tropism for gene therapy purpose.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to integrate the teachings of Nicklin et al., regarding use of adeno-associated virus (AAV) based vectors in gene therapy with the combined teachings of Tang et al., Turgeman et al., and Juan et al. regarding expressing a therapeutic gene from an adenoviral vector in a genetically modified mesenchymal stem cell, by substituting adenoviral vector taught by Juan et al. with an adeno-associated vector taught by Nicklin et al. to arrive at the claim 10 of instant application.

One having ordinary skill in the art would have been motivated to integrate the teachings of Nicklin et al. with the combined teachings of Tang et al., Turgeman et al., and Juan et al. because Nicklin et al teaches that both adenovirus (Ad) and adeno-associated virus (AAV) based vectors can be modified in tropism for gene therapy purpose.

There would have been a reasonable expectation of success given (i) the successful construction of double plasmid system and transfection/expression of the double plasmid system in rat embryonic cardiac myoplast cell line by the teachings of Tang et al., (ii) demonstration of genetically engineered human mesenchymal stem cells expressing human BMP-2 from an adenoviral vector leading to formation of cartilage and bone *in vivo* for treatment of osteoporesis by the teachings of Turgeman et al., (iii) the transfection and expression of Adv-OH-1 construct for gene therapy of atherosclerosis by the teachings of Juan et al., and (iv) demonstration of both adenovirus (Ad) and adeno-associated virus (AAV) based vectors can be modified in tropism for gene therapy purpose by the teachings of Nicklin et al. et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and response to Applicant's arguments are the same as documented in the rejection claims 1-9 and 11-19 under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (2002) in view of Turgeman et al. (2001) and Juan et al. (2001) in this office action.

Conclusion

7. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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